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Mendeleev Commun., 2024, **34**, 110–112

Mendeleev Communications

The reaction of acetylenes with aldazines in the NaOBu^t/DMSO system: a contribution to the pyrazole chemistry

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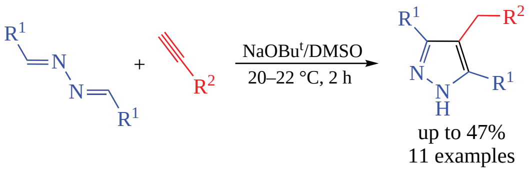
DOI: 10.1016/j.mencom.2024.01.033

Arylacetylenes readily react with aromatic aldazines in superbase medium NaOBu^t/DMSO (1 vol% EtOH) at room temperature to afford mainly 4-arylmethyl-3,5-diaryl-1*H*-pyrazoles in up to 47% yield along with minor amounts of 1-arylmethyl-3,5-diaryl-1*H*-pyrazoles and 1,2-diaryl-1,2-bis(3,5-diaryl-1*H*-pyrazol-1-yl)ethanes. The reaction is rationalized as proceeding *via* the diazaallyl anions, the adducts of acetylenic carbanions to a C=N bond, which further undergo the proton transfer processes and intramolecular cyclization to the above pyrazole derivatives.



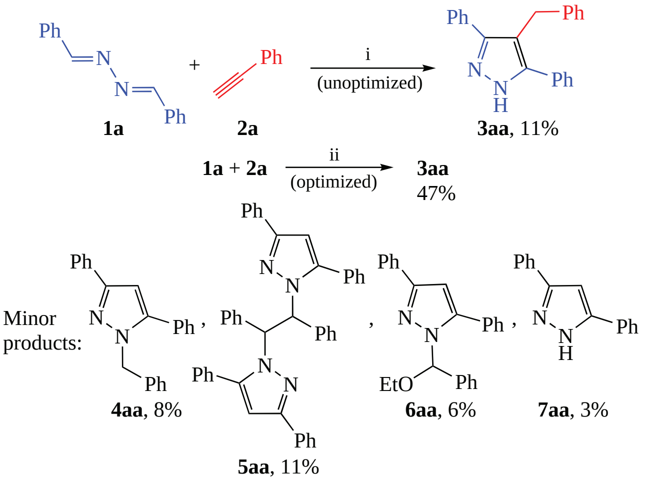
Keywords: acetylenes, azines, pyrazoles, superbases, ethynylation.

Acetylenes are known to be privileged starting materials in the synthesis of diverse carbo- and heterocyclic compounds.[1] Now the interest in the reactions of acetylenes promoted by superbases is rapidly growing.[2] Over few past years, attention is attracted to the recently discovered addition of acetylenic carbanions generated in superbase media to imines (C=N bonds).[3] The reaction happened to be substrate dependent divergent process providing a plethora of previously inaccessible nitrogen-containing products including propargylamines,[3] 1-azaalkadienes,[4] benzyl- and styryl-substituted imidazopyridines,[5] or diacetylenic bisamines.[6]

In this communication, we share the first results concerning the extension of this reaction over another class of imine substrates, aldazines, the compounds containing two C=N bonds linked *via* nitrogen atoms. Despite a number of existing publications[7] on the chemistry, structure, and applications of azines, their base-catalyzed reactions with acetylenes remain so far neglected.

The preliminary experiments showed that aldazine **1a** reacted with phenylacetylene **2a** in the presence of the superbase KOBu^t/DMSO under mild conditions (20 °C, 1 h) to afford 4-benzylpyrazole **3aa** as a major product in 11% yield, the reaction being accompanied by strong tar formation (Scheme 1). Formally, pyrazole **3aa** is a product of [4 + 1] cycloaddition, which so far remained unknown for azines.

Further optimization of the reaction conditions was carried out to evaluate the effect of superbase catalytic system (strong base/complexing solvent). It turned out that the formation of pyrazole **3aa** was observed (7–13% yields) when the process was conducted in KOH/DMSO, NaOBu^t/DMSO, and KOBu^t/DMSO systems, while the pair LiOBu^t/DMSO was inactive as well as the combination of NaOBu^t with DMF, THF, and 1,4-dioxane. Table 1 illustrates the influence of NaOBu^t concentration, temperature, reaction time, additives of alcohols, and order of the reactants feeding on the product yield and conversion of the starting **1a**. The higher and low content of the base compared to equimolar ratio of **1a**/NaOBu^t led to the drop of the product yield (entries 1, 2) and the conversion of **1a** (entry 3). The increase in temperature (40 °C, entry 4) and shortening the reaction time (entry 5) did not almost affect the process outcome. A considerable effect on the product yield was rendered by a small additive (1 vol% relative to DMSO) of ethanol that ensured 28% yield of 4-benzylpyrazole **3aa** (entry 6), though the same quantities of Bu^{t}OH had no impact on the reaction course (entry 7). Even much better yield (47%) was reached when azine **1a** was added dropwise (for 10 min) to a mixture of acetylene **2a** with NaOBu^t/DMSO containing 1 vol% of ethanol followed by 2 h stirring of the reaction mixture at room temperature (entry 10). From the reaction mixture, obtained under these conditions (entry 10), other minor pyrazole derivatives were isolated: 1-benzylpyrazole **4aa** (8%),



Scheme 1 *Reagents and conditions*: i, KOBu^t, DMSO, 20 °C, 1 h; ii, NaOBu^t, EtOH, DMSO, 20–22 °C, 2 h.

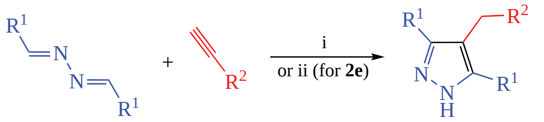
Table 1 Influence of NaOBu^t content, temperature and reaction time on the yield of **3aa**.[a]

Entry	**1a**/NaOBu^t molar ratio	Additive (vol%)	*t*/h	Conversion of **1a** (%)[b]	Yield of **3aa** (%)[b]
1	1:2	–	1	100	5
2	1:1	–	1	100	13
3	1:0.5	–	1	78	10
4[c]	1:1	–	1	100	8
5	1:1	–	0.25	100	9
6	1:1	EtOH (1)	1	99	28
7	1:1	Bu^{t}OH (1)	1	99	10
8	1:1	EtOH (2)	1	86	17
9[d]	1:1	EtOH (1)	1	97	32
10[d]	1:1	EtOH (1)	2	100	47
11[d,e]	1:1	EtOH (1)	2	98	42

[a] Conditions: a mixture of **1a** (1 mmol), **2a** (1 mmol), NaOBu^t, and DMSO (3 ml) was stirred at 20–22 °C for a specified time. [b] According to ^{1}H NMR of the crude product (durene was used as an internal standard). [c] At 40 °C. [d] Azine **1a** (1 mmol) in DMSO (2 ml) was added for 10 min to a mixture of **2a** (1 mmol), NaOBu^t and EtOH in DMSO (3 ml), and the reaction mixture was stirred for a specified time. [e] EtOH (60 μl), DMSO (6 ml).

1,2-bis(pyrazol-1-yl)-1,2-diphenylethane **5aa** (11%), 1-[ethoxy(phenyl)methyl]pyrazole **6aa** (6%), and 3,5-diphenylpyrazole **7aa** (3%) (see Scheme 1).

The synthesis under optimal conditions (see Table 1, entry 10) was proved to tolerate different aromatic aldazines **1a–g** and acetylenes **2a–d** as well as unsubstituted acetylene **2e** to provide the expected pyrazoles **3** in 14–47% yields (Scheme 2). The yields of pyrazoles **3** depend on the integrated effect of electronic and steric impact of the substituents both in aldazines and acetylenes, which is impossible to estimate separately. The stability of the starting aldazines (which were reported[8] to react with strong bases, albeit at 100 °C) and target pyrazoles as well as the formation of minor pyrazole derivatives of other chemotypes **4–7** also influence the reaction outcome. In particular, 'by-products' **4ea** and **5ab** were formed and isolated in reasonable yields of 38% and 21%, respectively, along with the target products **3ea** (14%) and **3ab** (44%) (see Scheme 2). Due to low yield, compound **3ea** could not be isolated pure and was only identified by ^{1}H NMR.

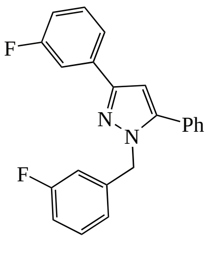


1a–g **2a–e** **3aa–ga** **3ab–ae**

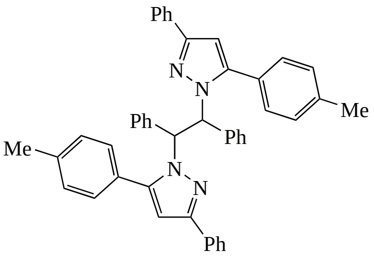
1a R^1 = Ph
1b R^1 = 3-MeC$_6$H$_4$
1c R^1 = 4-MeC$_6$H$_4$
1d R^1 = 3-MeOC$_6$H$_4$
1e R^1 = 3-FC$_6$H$_4$
1f R^1 = 2-furyl
1g R^1 = 2-thienyl

2a R^2 = Ph
2b R^2 = 4-MeC$_6$H$_4$
2c R^2 = 3-FC$_6$H$_4$
2d R^2 = 3-pyridyl
2e R^2 = H

3aa R^1 = R^2 = Ph, 47%
3ba R^1 = 3-MeC$_6$H$_4$, R^2 = Ph, 23%
3ca R^1 = 4-MeC$_6$H$_4$, R^2 = Ph, 43%
3da R^1 = 3-MeOC$_6$H$_4$, R^2 = Ph, 18%
3ea R^1 = 3-FC$_6$H$_4$, R^2 = Ph, 14%
3fa R^1 = 2-furyl, R^2 = Ph, 34%
3ga R^1 = 2-thienyl, R^2 = Ph, 15%
3ab R^1 = Ph, R^2 = 4-MeC$_6$H$_4$, 44%
3ac R^1 = Ph, R^2 = 3-FC$_6$H$_4$, 38%
3ad R^1 = Ph, R^2 = 3-pyridyl, 21%
3ae R^1 = Ph, R^2 = H, 15%



4ea, 38%
(formed along with **3ea**)



5ab, 21%
(formed along with **3ab**)

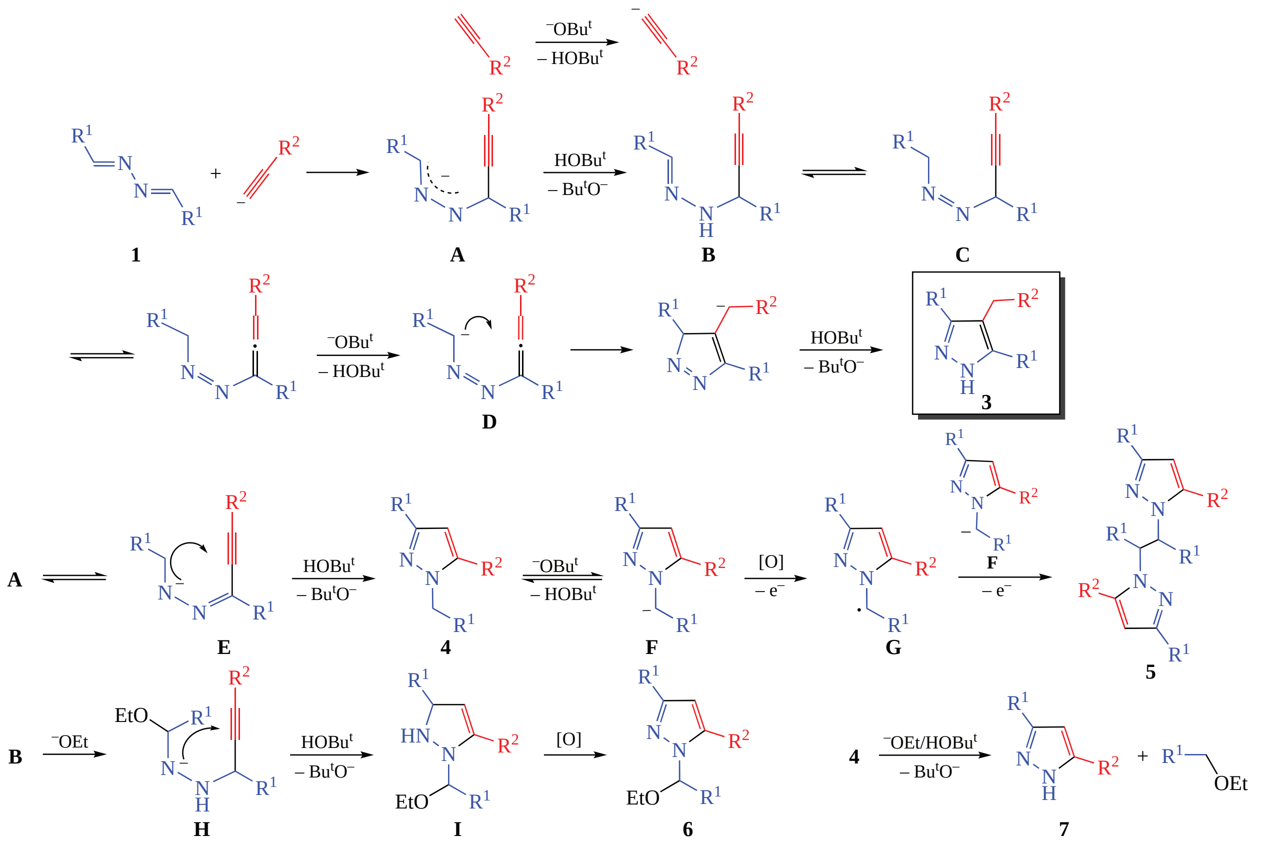
Scheme 2 *Reagents and conditions*: i, **1** (2 mmol) in DMSO (2 ml) was added for 20 min to a mixture of **2a** (2 mmol), NaOBu^t (2 mmol) and EtOH (60 μl) in DMSO (4 ml), 20–22 °C, 2 h; ii, the same in an autoclave, C_2H_2 **2e** pressure ~2 atm. Isolated yields after column chromatography are given except for **3ea** (from ^{1}H NMR).

Apparently, the acetylenic carbanions expectedly[3] are added to a C=N bond to generate diazaallyl anions **A**, which are neutralized by a proton of the medium (Scheme 3). The intermediate adducts **B**, after isomerization into adducts **C** and deprotonation of the CH_2 moiety, undergo the intramolecular cyclization *via* the attack of the forming carbanions **E** at the acetylenic fragment which can be present in the reaction mixture also in its allenic form to afford the major products **3**. Apart from this main reaction, the following branching transformations of the initial diazaallyl anions **A** likely occur. Their N-centered anionic isomers **E** may also undergo intramolecular cyclization to give pyrazoles **4**. This transformation (**E** → **4**) can be considered as a 5-*endo-dig* cyclization (often unfavorable process)[9] but, in this case, it may occur due to assistance of aromaticity of both the transition state and the product.[10] After the deprotonation of CH_2 group in **4** and oxidation (air oxygen or DMSO) of carbanions **F** formed, bispyrazole derivatives **5** are possibly produced by recombination of the corresponding radicals **G**. These bispyrazole derivatives **5** could also be generated by the reaction of radical **G** with relatively persistent anion **F** followed by quick oxidation of the initially formed dimeric radical anion. Such processes have been implemented recently for a variety of radical reactions under basic conditions.[11] The formation of ethoxybenzyl derivatives **6** may be explained by the initial attack of ethoxide anion at the C=N bond of intermediate hydrazones **B** to furnish anions **H** and their cyclization with spontaneous aromatization of dihydropyrazoles **I**. Pyrazoles **7** are probably resulted from the nucleophilic substitution of the benzyl moiety in pyrazoles **4** under the action of ethoxide (or *tert*-butoxide) anion.

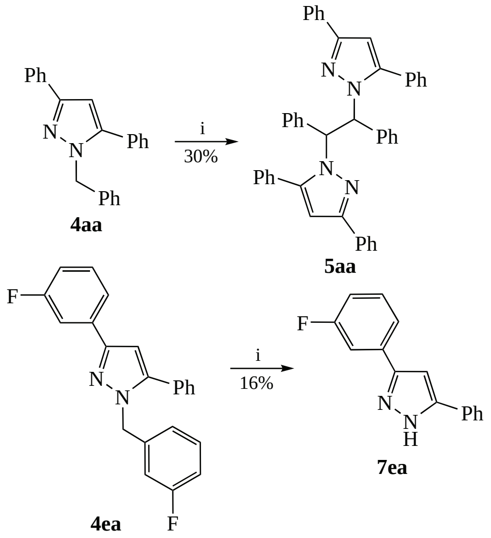
The route leading to bispyrazole derivative **5** was confirmed by its synthesis (in 30% yield) from 1-benzylpyrazole **4aa** under the reaction conditions (Scheme 4). Interestingly, fluorine-substituted pyrazole **4ea** did not undergo such a coupling. Instead, the corresponding pyrazole **7ea** is formed (see Scheme 4), probably due to a stronger polarization of C=N bond and a higher stability of the N-centered pyrazoline anion which behaves here as a leaving group.

Since acetylene **2a** and azine **1a**, when taken separately, almost are not changed under the reaction conditions, the strong tar formation, observed experimentally, evidences that the oligomerization of the anionic intermediates occurs. Therefrom it follows why the slow adding of azine **1** to the acetylene **2**/NaOBu^t/DMSO mixture provides better results. This is also in keeping with the experimental fact that the small additive of EtOH, a proton transfer agent, facilitates the cyclization by interrupting the oligomerization.

In summary, in this short communication, as a logic unfolding of the previously discovered acetylene carbanion addition to C=N bond,[3–6] we have shown that arylacetylenes are capable of easy reacting with aromatic aldazines in the NaOBu^t/DMSO superbase system at room temperature for a short time to deliver a bouquet of pyrazole derivatives in up to 75% total yield, mainly, 4-arylmethyl-3,5-diaryl-1*H*-pyrazoles. The reaction was rationalized in terms of intramolecular cyclization of acetylenic diazaallyl anions generated by the acetylenic carbanions addition to the C=N bond in the superbase medium. These preliminary findings are open to further optimization and represent a thought-stimulating contribution to the acetylene, azine, and pyrazole chemistry.



Scheme 3



Scheme 4 *Reagents and conditions*: i, NaOBu^t, DMSO, room temperature, 2 h.

This work was supported by the Russian Science Foundation (grant no. 19-13-00052). The spectral data were obtained with the equipment of the Baikal Analytical Center for collective use, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.033.

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Received: 14th August 2023; Com. 23/7225